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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	14

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,533	ARINI ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 13 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 69-80 are pending in the application.

Applicants' cancellation of claims 1 and 40-68 and addition of claims 69-80 in Paper No. 12, filed 01/03/03, is acknowledged. It is noted that applicants request cancellation of claims 1-68. However, claims 2-39 have been previously cancelled in Paper No. 9 (see page 5 of Paper No. 9).

Applicants' arguments in Paper No. 12 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restrictions

1. A restriction requirement was made grouping claims 1 and 40-68 into Groups I-VII (see item 1 of Paper No. 8). Applicants responded to the restriction requirement by electing with traverse Group I, claims 1-18 (page 5 of Paper No. 9). Due to amendment to the claims in Paper No. 9 to incorporate the limitations of the claims of Groups II and III into the claims of Group I, the examiner indicated that claims 1 and 40-55 would be co-examined (see item 2 of Paper No. 10). While the restriction of original claims 1-68 was made final, (see item 1 of Paper No. 10), applicants continue to traverse the restriction requirement in the instant response. Applicants traverse the restriction requirement (beginning at page 4 of Paper No. 12) by arguing that the inventions of Groups IV and V are linked to Groups I-III as process and product-by-process. Applicants assert that only a single search is required for examination of all claims of Groups I-V. Applicants' argument is not found persuasive.

MPEP 803 sets forth two criteria for restricting between patentably distinct inventions – 1) the inventions must be independent or distinct and 2) there must be a serious burden on the examiner. MPEP 803 states, "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie*

shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP 808.02". The invention of Group I is distinct from the inventions of Groups IV and V as set forth in items 5 and 6 of Paper No. 8, thus satisfying the first criterion for restriction. The invention of Group I is classified in 435/69.1, while inventions IV and V are classified in 424/94.63. Thus, the invention of Group I and the inventions of Groups IV and V have separate classification and therefore, the second criterion for restriction is satisfied. Thus, even though a search for the claims of Group I may overlap with the claims of Groups IV and V, the claims have separate classification and the criteria for restriction are satisfied. As stated in a previous Office action, (see item 1 of Paper No. 12) the requirement is still deemed proper and is therefore made FINAL. It is noted that the claims of Groups IV and V have been cancelled. Thus, applicants' argument regarding rejoinder of Groups I and IV and V is rendered moot.

Sequence Compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the specification at page 21 of the instant specification. See particularly 37 CFR 1.821(d). Applicants argue sequence identifiers have not been provided for the peptide sequences as disclosed at lines 20 and 22 of page 21 as the sequences do not identify any particular peptide, but represent only the results of Edman degradation. Applicants' arguments are not found persuasive. MPEP 2421.02 states, "The sequence rules embrace... ...all unbranched, non-D amino acid sequences with four or more amino acids" and "The rules apply to all sequences in a given application, whether claimed or not". There is no indication in the specification that

the peptide sequences disclosed at lines 20 and 22 of page 21 are branched or D-configuration amino acids. As such, the sequences should be identified by sequence identifiers.

Claim Objections

3. Claim 69 is objected to as being grammatically incorrect in the recitation of "to which has been added wherein with an alkanoic acid" in lines 7 and 8. It is suggested that applicants replace the term with "to which has been added an alkanoic acid".

4. Claims 69 and 73 are objected to as being grammatically incorrect in the recitation of "preproenzymes, zymogens, matrix metallo proteases" in claim 69 and "HEK-293, CV-1, COS, BSC-1, MDCK, A-431, CHO, BHK, CHO-Messi" in claim 73. It is suggested that applicants replace the terms with "preproenzymes, zymogens, and matrix metallo proteases" in claim 69 and "HEK-293, CV-1, COS, BSC-1, MDCK, A-431, CHO, BHK, and CHO-Messi" in claim 73.

5. In the interest of clarity, it is suggested that applicants insert the term "mature" prior to "protein precursor" in line 4 of claim 69 in order to identify the "protein precursor" as a "mature protein precursor".

Claim Rejections - 35 USC § 112, Second Paragraph

6. Claims 72, 75-78, and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 72 is indefinite in the recitation of "comprised from 0.1 to 20 mM". It is unclear from the claims and the specification as to the intended scope of alkanoic acid concentration. In order to clarify the claim, it is suggested that, for example, applicants remove the term "comprised" from the claim.

b. Claims 75 and 76 recite the limitation "said temperature". There is insufficient antecedent basis for this limitation in the claim. It is suggested that applicants clarify the meaning of the claim.

c. Claims 75 (claim 76 dependent therefrom), 77, 78, and 80 are confusing in that the claims recite "in step a)" in claims 75, 77, and 78 and "in step b)" in claim 80. However, there are no steps a) or b) in the claims from which 75, 77, 78, and 80 depend from. It is suggested that applicants clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

7. In view of applicants' amendment, the written description rejection of claims 1, 40, and 41, is withdrawn. The amendment has limited the precursor recombinant protein and encoding cDNA sequences therefor to preproenzymes, zymogens, and matrix metallo proteases.

8. The scope of enablement rejection of claims 69-80 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 14 of Paper No. 10).

Regarding the scope of preproenzymes, zymogens, and matrix metallo proteases produced by the claimed method, applicants argue (beginning at page 9 of Paper No. 12) the precursor recombinant protein as recited in the claims has been limited to preproenzymes, zymogens, and matrix metallo proteases. Applicants argue production of recombinant proteins is a routine method and the events underlying the production of recombinant mature proteins according to the invention are not specific to the particular expressed protein precursor. Applicants argue the ability of the butyrate to act as a processing enhancer is a general phenomenon since all precursor proteins as recited in claim 69 are activated by proteolytic cleavage and provide examples of such. Applicants argue cells used for protein expression are not "empty translational boxes", but process expressed proteins by way of endogenously expressed proteins. Applicants argue that, while the underlying mechanism for butyrate acting as a processing enhancer for mature protein expression was not provided in the instant specification, it is clear

that a 95 % active urokinase product is present. Applicants argue that, while only the processing of inactive urokinase to active urokinase due to the presence of butyrate was demonstrated in the specification, the method is applicable to other preproenzymes, zymogens, and matrix metallo proteases. Applicants argue the entire scope of the claimed invention is fully enabled in light of the working example provided in the specification combined with the knowledge of a skilled artisan. Applicants' arguments are not found persuasive. Undue experimentation would be required for a skilled artisan to make and use the entire scope of claimed methods. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). At the time of the invention, it appears that the ability of butyrate to act as a processing enhancer to facilitate the processing of inactive precursor proteins to an active form was not conventional in the art. This is evidenced by applicants' disclosure in the specification at page 5, lines 6-9, "To the best of our knowledge this is the first time that alkanoic acids... ...are used as 'processing enhancers' of precursor proteins as defined above". The specification provides no guidance as to the mechanism of butyrate acting as a "processing enhancer" to indicate that this is a general phenomenon common to all precursor proteins. The specification has provided guidance in the form of only a single working example of butyrate acting as a "processing enhancer" for processing single chain urokinase to two chain urokinase. There are many factors to consider in making a determination as to whether butyrate processing enhancement is a specific or general event. One of skill in the art recognizes that the processing of precursor proteins to their corresponding active proteins is specific to a particular processing enzyme and the cleavage site of an enzyme to be processed. Butyrate is known to induce the activity of transcription factors such as Cdx2 (see Domon-Dell et al. Gut 50:525-529) and has been shown to activate gene expression (see Okabayashi Cell Struct Funct 14:579-586). Therefore, one of skill in the art may reasonably expect enhanced processing of urokinase to be due to butyrate-induced

expression of a processing enzyme that is urokinase-specific and is not involved in processing other preproenzymes, zymogens, and matrix metallo proteases as broadly encompassed by the claims. Furthermore, because the urokinase is recombinantly expressed, there remains the possibility that butyrate processing enhancement is an artifact of the combination of cell line, plasmid, and culture medium. In this regard, as guidance has not been provided as to whether this event is general or specific, further experimentation would be required in order to determine if processing of other preproenzymes, zymogens, and matrix metallo proteases as broadly encompassed by the claims could be similarly enhanced by the presence of butyrate in the medium. As guidance regarding the effect (specific or general) of processing of other preproenzymes, zymogens, and matrix metallo proteases has not been provided, one of skill in the art would recognize there exists substantial uncertainty as to whether this is a general or specific event.

Regarding the scope of alkanoic acids applicants argue claim 69 has been limited to specific alkanoic acids. To the extent the rejection applies to the scope of alkanoic acids, the scope of alkanoic acids as recited in claim 69 would appear to be enabled based on the usage of such alkanoic acids for protein expression as is known in the art.

Regarding the scope of ion exchange matrices and buffers, applicants argue the isoelectric point of urokinase is known in the art and based on the knowledge of protein purification provided in the art, a skilled artisan would not require guidance as to a *specific* ion exchanger. Applicants' arguments are not found persuasive. As stated in a previous Office action, the specification does not establish a rational and predictable scheme for using *any* ion exchange matrix with an expectation of obtaining the desired protein using an elution buffer for elution of LMW tc-uPA comprising *any* monovalent ion (anionic or cationic) concentration between 200 and 300 mM, and an elution buffer for elution of HMW tc-uPA comprising *any* monovalent ion (anionic or cationic) concentration of at least 400 mM the buffer. One of skill in the art would recognize that the ability of an ion exchange matrix to purify a protein is dependent upon the ion concentration of the elution buffer and *any* ion exchange matrix will not necessarily be useful for purification of LMW and HMW using elution buffers with *any* monovalent ion concentration as

recited in claim 43 parts d) and e). Therefore, without further guidance, the specification is only enabling for purification of LMW and HMW tc-uPA using SP-Sepharose (as disclosed in the specification at page 19). The elution of a particular protein, even though its isoelectric point is known, is dependent upon the combination of ion exchange matrix (anionic or cationic) and the concentration of the elution buffer. The specification provides guidance in the form of only a single working example of such a combination – an SP-Sepharose cationic matrix using NaCl as the elution buffer. As claim 71 is not so limited to a particular ion exchange matrix – it can be either anionic or cationic – and is not limited to a particular elution buffer, based on the guidance provided in the specification, there remains a high degree of unpredictability that the recited proteins could be purified using a buffer having the recited concentrations and further guidance is necessary for a skilled artisan to successfully purify the recited proteins using buffers having the recited concentrations.

Claim Rejections - 35 USC § 102

9. The rejection of claims 69 and 70 under 35 U.S.C. 102(b) as being anticipated by Okabayashi et al. (Cell Struct Funct 14:579-586, 1989; hereafter referred to as "Okabayashi") is maintained for the reasons of record and the reasons stated below. The rejection as it applied to claims 1 and 40-42 was fully explained in a previous Office action (see item 15 of Paper No. 10).

Applicants argue (beginning at the top of page 12 of Paper No. 12) the reference of Okabayashi does not disclose whether the urokinase produced is active or inactive as the method of Okabayashi for assaying urokinase activity (page 581 bottom to page 582 top) does not distinguish between the active form (two chain urokinase) and the inactive form (single chain urokinase) of the enzyme and is useful only for measuring total urokinase. Applicants argue that since plasmin converts single chain urokinase into two chain urokinase, the urokinase assay of Okabayashi intrinsically converts single chain urokinase into two chain urokinase and therefore, there is no way of determining whether the urokinase expressed by in the method of Okabayashi is active or inactive. Applicants argue that the instant specification discloses (page 5, lines 3-9) that butyrate analogues act as processing enhancers favoring or enhancing

the maturation of recombinant proteins with the need for external proteolytic enzymes. Applicants argue their assay for measuring urokinase activity distinguishes between active and inactive urokinase and demonstrates that their method for measuring urokinase activity indicates that 95 % of the total urokiase is mature, active urokinase. Applicants' argument is not found persuasive. Addressing the urokinase activity assay of Okabayashi, there is no disclosure by Okabayashi of plasmin being a component of the assay. Instead, Okabayashi list the components of the assay as plasminogen and fibrin. In the urokinase assay of Okabayashi, a plasminogen activator, in this case mature, catalytically active, two chain urokinase, converts plasminogen to plasmin, which in turn degrades fibrin resulting in a clear zone of lysis which can be correlated to the amount of plasminogen activator (two chain urokinase) present in the sample (see page 582, lines 1-7). Thus, in order for fibrin to be cleaved by plasmin, plasminogen must first be converted to plasmin by the presence of (catalytically active) two chain urokinase. Because plasmin was not initially present in the assay components, two chain urokinase *must have been present* in order to initiate cleavage of plasminogen. Therefore, in the absence of any evidence that plasmin *was* present in the urokinase assay of Okabayashi, one must conclude that mature (two chain) urokinase was produced by the method of Okabayashi. Furthermore, applicants have provided no characteristics to distinguish their claimed method from the method of Okabayashi. In fact, the reference of Okabayashi need not disclose that the produced urokinase was in an active form, as this would have been an inherent characteristic of the urokinase produced by the method of Okabayashi due to the presence of butyrate in the culture medium.

Addressing the differences in the effects of butyrate as described by Okabayashi and the instant application, the claims are not so limited to specific effects due to the presence of butyrate in the culture medium. In other words, there is no limitation provided in the claims that the effect of butyrate is processing of a recombinant protein into an active or mature form. The limitation is only that an alkanoic acid (of claim 69) be added to the culture medium. While Okabayashi indicates the effect of butyrate is an increase of transcription and/or translation (page 584, bottom first full paragraph), the limitation of supplementing the culture medium with butyrate is clearly disclosed by Okabayashi. Thus, applicants

argue limitations that are not present in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As such, the cited reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

10. The rejection of claims 71-76 and 80 under 35 U.S.C. 103(a) as being unpatentable over Okabayashi in view of Nobuhara et al. (J Biochem 90:225-232, 1981; hereafter referred to as "Nobuhara"), and Miwa et al. (Chem Pharm Bull 29:463-471, 1981; hereafter referred to as "Miwa") is maintained for the reasons of record and the reasons stated below. The rejection as it applied to claims 43-49 and 53-55 was fully explained in a previous Office action (see item 16 of Paper No. 10).

Applicants argue (beginning at page 14 of Paper No. 12) Okabayashi has been distinguished from the claimed invention as there is no teaching by Okabayashi that the cell supernatant contains two chain urokinase as a consequence of the addition of butyrate to the culture medium. Applicants argue that based on the absence of a teaching by Okabayashi showing a ratio of active to inactive urokinase combined with the teaching of Hu (cited in item 9 below) that 90 % of recombinantly produced urokinase is inactive, one of ordinary skill in the art would have derived that the addition of butyrate increases the production of inactive urokinase. Applicants argue their effect due to butyrate is different and totally unexpected from the teaching of Okabayashi. Applicants argue the Nobohara reference discloses a comparison of high molecular weight and low molecular weight urokinase. Applicants' arguments are not found persuasive. Regarding applicants' argument addressing the reference of Nobohara, this reference teaches purification of high and low molecular weight urokinase, which is well known to one of ordinary skill in the art (for a detailed description of the teachings of Nobohara, see item 16, paragraph 3 of Paper No. 10) and is more than just a comparison of high and low molecular weight urokinase. Regarding applicants' arguments addressing differences between the descriptions of effects of butyrate on protein production by Okabayashi and the instant application, as stated in item 7 above, the claims are not so

limited to specific effects due to the presence of butyrate in the culture medium. There is no limitation provided in the claims for a particular level of mature protein. Although Hu demonstrates that 90 % of the expressed urokinase is inactive, an ordinarily skilled artisan would recognize that 10 % of the urokinase is in its active form. As such, Hu does not teach away from the claimed invention. Thus, applicants argue limitations that are not present in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, as stated above, applicants have provided no characteristics to distinguish their claimed method from the method of Okabayashi. In fact, the reference of Okabayashi need not disclose that the produced urokinase was in an active form, as this would have been an inherent characteristic of the urokinase produced by the method of Okabayashi due to the presence of butyrate in the culture medium.

Applicants argue (beginning at page 15, first full paragraph) production of mature recombinant proteins may represent a major problem because the recombinant protein is not physiologically activated. Applicants argue claim 71 recites a method for purification of two chain urokinase in a single chromatographic step. Applicants argue this contrasts with the reference of Miwa that discloses a three-step purification of urokinase. Applicants argue the concentration of urokinase in the starting material is also different between Miwa and the instant application and thus, one of ordinary skill in the art would be directed away from the teachings of Miwa. Applicants argue their method of a single step purification of high molecular weight and low molecular weight urokinase could not be derived from the cited references. Applicants' arguments are not found persuasive. Again, applicants argue limitations that are not present in the claims. There is no indication in claim 71 that the method is limited to a *single* step purification procedure. In fact, the use of "comprising" language expressly allows additive steps. As written, it would appear the method is not limited to a single step as claim 69 from which claim 71 depends recites, "A process for the production of a mature recombinant protein... ...comprising incubating said cell line..." This would appear to indicate that the method of claim 71 is not limited to the chromatography steps as set forth therein, but *comprises* these steps. As stated in a previous Office

action, methods of purifying low molecular weight and high molecular weight urokinase by ion exchange chromatography are well known in the prior art as exemplified by the references of Nobahara and Miwa and because these proteins are commercially and physiologically relevant, there is motivation for purifying these proteins. As previously stated, while the examiner recognizes that neither Nobuhara nor Miwa teaches a purification scheme or buffers used for elution of the HMW and LMW forms of tc-uPA as specifically recited in the claims, one of ordinary skill in the art would have recognized that the buffers used for a particular chromatography would depend on such factors as the specific chromatography matrix, the manufacturer's recommendations, and the relative stability of the desired protein. Therefore, it is clear from the cited representative prior art references that methods of isolating HMW and LMW tc-uPA using various combinations of chromatography matrices in differing orders with different buffers were well known to one of ordinary skill in the art. Thus, based on the state on the prior art, it is well within the ability of an ordinarily skilled artisan to purify HMW from LMW forms of tc-uPA using ion exchange chromatography and optionally benzamidine chromatography and gel filtration chromatography using the buffers as recited in the claims. As such, the cited references render obvious the claimed invention.

11. The rejection of claims 77-79 under 35 U.S.C. 103(a) as being unpatentable over Okabayashi in view of Nobuhara, and Miwa as applied to claims 71-76 and 80 above, and further in view of Hu et al. (Sheng Wu Gong Cheng Xue Bao 16:387-391, hereafter referred to as "Hu") is maintained for the reasons of record and the reasons stated below. The rejection as it applied to claims 50-52 was fully explained in a previous Office action (see item 17 of Paper No. 10).

Applicants argue (beginning at page 16 of Paper No. 12) Hu discloses that 90 % of their urokinase was inactive, while the instant specification discloses that greater than 95 % of applicants' urokinase was active. Applicants argue that since one cannot infer from the reference of Okabayashi that acive urokinase can be obtained through the use of butyrate, it would not be obvious to combine the cited references. Applicants' arguments are not found persuasive. Again, applicants argue a limitation – in this case a particular level or pecentage of mature protein - that is not present in the claims. The claims

are not so limited to a particular level or percentage of active protein. Thus, applicants argue a limitation that is not in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, as stated above, applicants have provided no characteristics to distinguish their claimed method from the method of Okabayashi. In fact, the reference of Okabayashi need not disclose that the produced urokinase was in an active form, as this would have been an inherent characteristic of the urokinase produced by the method of Okabayashi due to the presence of butyrate in the culture medium. As such, the cited references render obvious the claimed invention.

Conclusion

12. No claim is in condition for allowance.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600